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REVIEW ARTICLE

When should a liver resection be performed in patients with liver metastases from neuroendocrine tumours? A systematic review with practice recommendations

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Abstract

Aim: To determine the benefits and risks of hepatic resection versus non-resectional liver-directed treatments in patients with potentially resectable neuroendocrine liver metastases.

Methods: A systematic review identified 1594 reports which alluded to a possible liver resection for neuroendocrine tumour metastases, of which 38 reports (all retrospective), comprising 3425 patients, were relevant.

Results: Thirty studies reported resection alone, and 16 studies reported overall survival (OS). Only two studies addressed quality-of-life (QoL) issues. Five-year overall survival was reported at 41–100%, whereas 5-year progression-free survival (PFS) was 5–54%. We identified no robust evidence that a liver resection was superior to any other liver-directed therapies in improving OS or PFS. There was no evidence to support the use of a R2 resection (debulking), with or without tumour ablation, to improve either OS or QoL. There was little evidence to guide sequencing of surgery for patients presenting in Stage IV with resectable disease, and none to support a resection of asymptomatic primary tumours in the presence of non-resectable liver metastases.

Conclusion: Low-level recommendations are offered to assist in the management of patients with neuroendocrine liver metastases, along with recommendations for future studies.

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Introduction

Neuroendocrine tumours (NETs) frequently metastasise to the liver. Numerous treatment options have been used both for cure and disease control. Surgical treatment consists of curative resection, palliative cytoreductive resection and transplantation. Owing to various factors, a complete surgical resection is possible only in a minority of people with neuroendocrine liver metastases (NLMs). Ablative therapies may also be used, either as an adjunct to surgery or as a primary treatment. A hepatectomy is the only potentially curative treatment for NLMs, but there are few prospective studies comparing modalities of treatment.[1] A Cochrane review[2] concluded that there was insufficient evidence comparing surgical resection to other treatment modalities, and therefore surgical resection remains the standard of care whenever possible.

Hepatic metastases occur in 50–75% of patients with NET. A complete resection of such hepatic metastases is feasible in only 7–15% of patients.[3] Until now, surgical management was considered the best approach for resectable hepatic metastases from NET in terms of symptom relief and prolonged survival, in spite of the high incidence of recurrence after surgery.[4] Advances in technology have led to the development of new liver-directed therapies including ablative techniques, transarterial chemoembolization (TACE) or selective internal radiation therapy (radioembolization), which have been shown to be effective in slowing tumour progression and

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palliating symptoms.[5,6] The treatment of hepatic metastases from NET has therefore evolved into a more diverse multimodal approach, where the role of surgery should be reappraised.

The aim of this review was to determine the benefits and risks of a hepatic resection versus non-resectional liver-directed treatments in patients with potentially resectable NET liver metastases. Since this work was done in the context of the 2012 international consensus conference on NLMs in London, it does not cover the role of liver transplantation which was reviewed by another expert group and published separately.

Materials and methods

Definitions

Resectability of NET tumour metastatic to the liver depends on both technical-anatomic considerations and also on tumour biology. There is general agreement that a liver resection for metastatic NET should be considered as a debulking procedure.[7] As a consequence, the assessment of resectability of liver metastases from NET can lead to different conclusions depending on technical judgment regarding anatomic versus non-anatomic removal of all tumour deposits, or in the general setting of a hepatic resection when the natural history of the disease is taken into account. In this review, unless otherwise specified, resectability is intended to be the removal of all NET metastases within the liver parenchyma by means of surgical interventions with curative intent.

Methods

Since this review was prepared for the 2012 international consensus conference on NLMs in London, the literature search was organized and centralized by the organizing committee of the conference. Librarians of the Medical Library Careum, University of Zurich, Switzerland, developed the electronic search strategy to query databases and to identify all potentially relevant articles. The following databases were searched: Medical Literature Analysis and Retrieval System Online, Excerpta Medica Database, and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials). Titles and/or abstracts of all identified records were independently screened by two members of the review team to ascertain their relevance. The full text of each of these potentially relevant studies was then assessed for eligibility. Any disagreement was resolved through discussion with a third review team member. Additional articles were retrieved through manual search or scanning of reference lists. No language or publication date restrictions were imposed on the literature search.

The participants/population studied included patients who underwent hepatic surgery, or any other treatment for resectable hepatic metastases from NET. Studies that did not report overall survival (OS) were excluded. The intervention(s), exposure(s) reviewed included: hepatic resection, local ablative techniques, peptide receptor radionuclide treatment, chemotherapy and biotherapy. The primary outcome considered was OS after treatment for resectable hepatic metastases from NET, with secondary outcomes including progression-free survival (PFS) and quality of life (QoL).

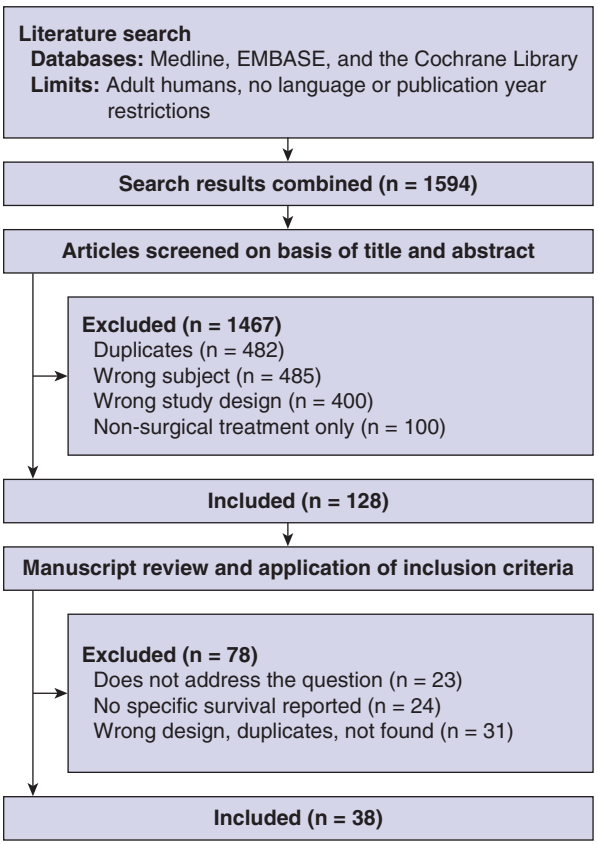

Figure 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart showing selection of the studies for review

Level of evidence and strength of recommendation were graded according to the grades of recommendation, assessment, development and evaluation (GRADE) system, which allows a separate rating of the quality of evidence and grading for the strength of recommendations.[8] It offers four levels of evidence quality: high, moderate, low and very low.

The systematic reviews were prospectively registered with the International Prospective Register of Systematic Reviews CRD42012002652[9] and the study methodology adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The full research strategy was published elsewhere.[10]

Results

Figure 1 shows the flow chart of study selection. From a total of 1594 studies identified by the search strategy, 38 studies were included in this review. No studies were randomized controlled trials. All of them were retrospective including 11 comparative

Table 1 Retrospective studies comparing liver resection with other treatments for neuroendocrine liver metastases

Authors, year	Total no. of patients	Treatment groups (no. of patients)	OS median (months) 5 year (%)	PFS median (months)
Saxena *et al*., 2012[a19]	17	Liver resection (10)	79	22
		Radioembolization (15)	NR	18
		Systemic chemotherapy (14)	18	6
		Conservative therapy (11)	59	16
Karabulut *et al*., 2011[13]	123	Liver resection (29)	190	15
		RFA (69)	73	10.5
		Embolization (29) (TAE, TACE or SIRT)	33	6.5
Mayo *et al*., 2011[16]	753	Liver resection (339)	74%	NA
		Intra-arterial therapy (414) (TAE, TACE, SIRT)	30%	NA
Landry *et al*., 2008[14]	54	Liver resection ± ablation (23)	75%	NA
		No liver resection (31)	62%	NA
Musunuru *et al*., 2006[17]	48	Liver resection ± RFA (13)	83% (3-year OS)	NA
		Embolization (18)	31% (3-year OS)	NA
		Conservative (17)	31% (3-year OS)	NA
Osborne *et al*., 2006[18]	120	Cytoreduction (61)	43 (mean OS)	NA
		Embolization (59)	24 (mean OS)	NA
Touzios *et al*., 2005[20]	60	Liver resection ± ablation (19)	72%	NA
		TACE ± resection (18)	50%	NA
		Conservative (23)	25%	NA
Yao *et al*., 2011[21]	36	Liver resection (16)	70%	NA
		TACE (20)	40%	NA
Chamberlain *et al*., 2000[11]	85	Liver resection (34)	76%	NA
		Embolization (33)	50%	NA
		Conservative (18)	39% (3-year OS)	NA
Chen *et al*., 1998[12]	38	Liver resection (15)	73%	NA
		Conservative (23)	29%	NA

NR, not reached; NA, not available.
[a]Saxena *et al*. compared different types of treatments of liver recurrence after initial surgery.
OS, overall survival; PFS, progression-free survival; TAE, transarterial embolization; TACE, transarterial chemoembolization; RFA, radiofrequence ablation; SIRT, Selective internal radiation therapy.

cohort studies[11–21] and 27 case-series.[7,22–47] Overall, 20 studies were performed in USA, 14 in Europe (7 in France, 4 in Germany, 2 in UK, 1 in Italy), 3 in Australia and 1 in Japan, comprising 3425 patients. Thirty studies (79%) included a group of patients who only underwent a hepatic resection. In the other studies, hepatic resections were always combined with either radiofrequency ablation (RFA) or cryoablation, which confounds interpretation of reported outcomes. Only 16 studies (42%) reported 5-year OS and only 5 (13%) reported 5-year PFS. Quality of life after surgery was assessed formally in only two studies.[18,36] After a hepatic resection alone, 5-year survival was reported between 41% and 100%, and 5-year PFS between 5% and 54%.

Does potentially curative (R0) resection improve OS?

Is there any evidence to suggest that a hepatic resection with curative intent (R0/R1) improves outcomes (tumour-free survival, OS, QoL) for patients with resectable NLMs, when compared with non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy or biotherapy)?

When considering a liver resection for these patients, the points to be considered include selection bias of patients reported undergoing a liver resection, defining R0 resection and an acceptable definition of 'debulking' (and what would be considered acceptable in terms of symptom control?), and the comparator procedures including transplantation.

As shown in Table 1, only 10 studies compared a hepatic resection with other treatments for resectable hepatic metastases from NET,[11–14,16–21] and only 3 of these studies reported more than 100 patients.[13,16,18] All of these studies were retrospective and uncontrolled. Consequently, patient groups were heterogeneous in most

of these studies. In four studies, patients included within the hepatic resection groups actually underwent a partial hepatectomy and ablation,[14,17,20] or resection was considered incomplete (cytoreduction).[18] In most studies combining resection and embolization, patients underwent either transarterial embolization (TAE), TACE or radioembolization.[11,13,16–18] Finally, patients included in the conservative or non-resection treatment groups underwent either chemotherapy, radiotherapy or received octreotide.

All studies suffered from a bias of patient selection. Indeed, patients who underwent non-surgical treatment had a greater tumour burden, larger tumours and a higher incidence of bilobar disease. Therefore, the relatively greater survivals reported after a surgical resection compared with patients who underwent embolization or conservative treatment should be interpreted with caution. Four studies showed significantly greater OS after a hepatic resection compared with other treatments, but only with univariate analysis.[12,17,18,20] With multivariate analysis, the type of treatment was never associated with improved survival. Of note, the most frequent and significant adverse correlate of survival was the presence of extra-hepatic disease.[13,16,19]

A comparison of PFS between treatment groups was only available in two studies.[13,19] Saxena *et al.*[19] showed that independent factors for PFS included histological grade, extra-hepatic disease and type of treatment. However, these series focused on the management of a hepatic recurrence of metastatic NET after initial surgical treatment. In the study by Karabulut *et al.*,[13] treatment modality was neither an independent factor for PFS or OS. Only one study assessed QoL among treatment groups using the patient's Eastern Cooperative Oncology Group (ECOG) performance status.[18] Patients who underwent embolization had a significant decrease in performance status after treatment compared with patients who underwent cytoreductive surgery. However, patients who underwent embolization had more diffuse hepatic disease.

In conclusion, although a hepatic resection is currently the mainstay of curative treatment for resectable metastases from NET, there is no robust evidence that it is superior to other liver-directed or systemic therapies (GRADE level of evidence: low).

Is there a role for R2 (debulking) surgery?

Does a R2 hepatic resection (debulking) improve the outcome (PFS, OS, QoL) in patients with NET liver metastases, when compared with non-surgical treatment (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, targeted therapy or biotherapy)?

Only one study was identified which addressed this question.[18] In the study by Osborne *et al.*,[18] 38 patients underwent a curative resection, 23 had cytoreductive surgery (R2) and 59 were treated with TAE. Considering patient selection bias, the mean survival in patients who underwent palliative cytoreduction was 32 compared with 24 months in patients treated with embolization ($P < 0.001$). Patients who underwent curative surgery had the best mean survival (50 months). As stated previously patient performance status after treatment was worse in the embolization group.

There is no evidence that a R2 hepatic resection improves survival or QoL when compared with TAE (GRADE level of evidence: low). No comparison is available between a R2 liver resection and peptide receptor radionuclide treatment.

Is there any role for tumour ablation as an adjunct to R2 (debulking) surgery?

In patients with hepatic metastases from NET, do locally ablative techniques as an adjunct to a R2 liver resection improve outcome (PFS, OS, QoL)?

We did not identify any study which may answer this question. There is no evidence that locally ablative techniques, as an adjunct to a R2 hepatic resection, improve the outcome of patients with hepatic metastases from NET (GRADE level of evidence: nil).

Sequencing of surgery for primary and metastases if both resectable

In patients with both synchronously resectable primary NET and hepatic metastases, should the primary or the hepatic metastases be resected first or together to improve outcome (PFS, OS, QoL)?

There is no comparative study designed to answer this specific question. However, some data can be extracted from retrospective studies.[11,16,21,22,29,47] Four studies reported that an initial resection of the primary NET was associated with prolonged survival on univariate analysis.[11,16,21,22] In two of these studies,[16,22] an initial resection of the primary NET remained an independent factor associated with survival on multivariate analysis. Only one study did not show any benefit on survival of resection of the primary NET, but the small number of patients who did not have resection of their primary NET precluded a definitive conclusion on the impact of a resection of the primary NET on survival.[47]

More recently, Gaujoux *et al.*[29] showed in a series of 36 patients that synchronous resection of a primary tumour and hepatic metastases can be performed with low mortality (3%). Additionally, most patients developed recurrence in the liver which was amenable to subsequent ablative therapies allowing on-going disease control. There are no studies which address the outcome of a hepatic resection of metastatic NET first before subsequent resection of the primary NET on survival.

Little evidence suggests that resection of the primary NET in patients with resectable hepatic metastases improves survival. There is insufficient data to support whether resection of the primary NET, either initial to or concomitant with resection of hepatic metastases, affects outcomes (GRADE level of evidence: low).

Recommendations

Hepatic resection has been widely employed for metastatic NET. Current data show that a hepatic resection of metastatic NET, whether metachronous to, or synchronous with resection of the primary NET, can be performed with limited and clinically

acceptable operative risk. However, the efficacy of such treatment, based either on comparative non-operative controls or alternative non-resective treatments on similarly matched patient cohorts, remains unproven.

Hepatic resection with/without ablation could be offered to patients with liver limited/dominant metastatic NETs with intended curative/long-term survival benefit provided they fulfil the following criteria (Level of recommendation: Low):

1 The primary tumour is resected or resectable (along with any possible draining lymph node involvement).
2 The patient is both fit for and willing to consider a hepatic resection (and in particular has no significant untreated carcinoid cardiac disease that would preclude a safe hepatic resection).
3 The liver disease can be macroscopically resected/ablated with the preservation of enough functional disease-free liver remnant according to the body surface area of the patient.
4 All identified hepatic disease can be resected/ablated with curative intent.

Future reports addressing hepatic resection for metastatic NET should include:

a. Details regarding resection of the primary NET – site, type of resection, local-regional stage of the primary NET, date of resection of the primary NET, type of interim therapy before resection of hepatic metastases if metachronous presentation of the latter and timing from initial diagnosis of NET, functional status of the primary NET.
b. The development of a quantitative (or at least semi-quantitative) hepatic staging system to provide a rational basis for future treatment protocols and outcome assessment. Similarly, regarding R1 versus R2 resection definitions.
c. Details regarding resection of the metastatic NET – type of hepatic resection, extent of hepatic resection (R0, R1, R2), descriptors of R2 disease, type of concurrent ablative treatments, extent of combined treatments (R0, R1, R2), presence or absence of extrahepatic metastases, mechanism of documentation of extrahepatic disease (imaging, intra-operative observation, biopsy, etc).
d. Details of adjunctive treatments – type and number of non-resective treatments, indication for non-resective treatment (neoadjuvant, adjunctive, adjuvant).
e. Development of a registry based on the recommended database so that prospectively acquired data can be generated to detail operative risks and outcomes. This database should also be used for comparative studies of multimodality therapy.

Conflicts of interest

None declared.

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